

EXHIBIT 11

PROP

PHYSICIANS FOR RESPONSIBLE OPIOID PRESCRIBING

2012 JUL 25 P 1:48

PRESIDENT
ANDREW KOLDONY, MD
BROOKLYN, NY

VICE PRESIDENT
MICHAEL VON KORFF, SCD
SEATTLE, WA

TREASURER
ROSEMARY ORR, MD
SEATTLE, WA

SECRETARY
STEPHEN GELFAND, MD
MYRTLE BEACH, SC

JANE BALLANTYNE, MD
SEATTLE, WA

IRFAN DHALLA, MD, MSC
TORONTO, ON

GARY FRANKLIN, MD, MPH
SEATTLE, WA

PETE JACKSON
ARLINGTON HEIGHTS, IL

DAVID JUURLINK, MD, PhD
TORONTO, ON

PETROS LEVOUNIS, MD, MA
NEW YORK, NY

LEN PAULozzi, MD, MPH
ATLANTA, GA

JON STRELTZER, MD
HONOLULU, HI

BETTS TULLY
CHICAGO, IL

ART VAN ZEE, MD
ST. CHARLES, VA

July 25, 2012

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville MD 20852

The undersigned clinicians, researchers and health officials from fields that include Pain, Addiction, Primary Care, Internal Medicine, Anesthesiology, Psychiatry, Neurology, Emergency Medicine, Toxicology, Rheumatology, and Public Health submit this petition under Section 21 CFR 10.20 and 21 CFR 10.30 and other pertinent sections of the Federal Food, Drug and Cosmetic Act or any other statutory provision which authority has been delegated to the FDA Commissioner to regulate labeling of opioid analgesics.

At present, the FDA-approved indication for nearly all instant-release opioid analgesics is "moderate to severe pain". For extended-release opioids, the indication is for "moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." These overly broad indications imply a determination by FDA that they are safe and effective for long-term use. As outlined below, an increasing body of medical literature suggests that long-term use of opioids may be neither safe nor effective for many patients, especially when prescribed in high doses.

Unfortunately, many clinicians are under the false impression that chronic opioid therapy (COT) is an evidence-based treatment for chronic non-cancer pain (CNCp) and that dose-related toxicities can be avoided by slow upward titration. These misperceptions lead to over-prescribing and high dose prescribing. By implementing the label changes proposed in this petition, FDA has an opportunity to reduce harm caused to chronic pain patients as well as societal harm caused by diversion of prescribed opioids. In addition, FDA will be able to reinforce adherence to dosing limits that have been recommended by the United States Centers for Disease Control¹, the state of Washington² and the New York City Department of Health and Mental Hygiene³.

The Federal Food, Drug and Cosmetic Act established that a drug intended to treat a condition must be proven safe and effective for use as labeled.⁴ The current label on opioid analgesics does not comply with this law. By taking the actions requested in this petition, FDA will be able to exercise its regulatory responsibility over opioid manufacturers by prohibiting the marketing of opioids for conditions in which their use has not been proven safe and effective.

FDA 2012.P.0818

CP

SPECIFIC ACTIONS REQUESTED FOR CHANGES TO OPIOID ANALGESIC LABELS:

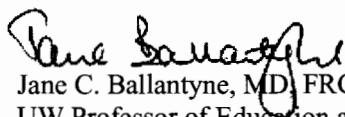
1. Strike the term “moderate” from the indication for non-cancer pain.
2. Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain.
3. Add a maximum duration of 90-days for continuous (daily) use for non-cancer pain.

STATEMENTS OF SCIENTIFIC BASIS FOR PETITION:

1. Over the past decade, a four-fold increase in prescribing of opioid analgesics has been associated with a four-fold increase in opioid related overdose deaths and a six-fold increase in individuals seeking treatment for addiction to opioid analgesics.⁵
2. Prescribing of opioids increased over the past 15 years in response to a campaign that minimized risks of long-term use for CNCP and exaggerated benefits.^{6,7,8}
3. Long-term safety and effectiveness of managing CNCP with opioids has not been established.⁹
4. Recent surveys of CNCP patients receiving COT have shown that many continue to experience significant chronic pain and dysfunction.^{10,11}
5. Recent surveys using DSM criteria found high rates of addiction in CNCP patients receiving COT.^{12,13}
6. A large sample of medical and pharmacy claims records found that two-thirds of patients who took opioids on a daily basis for 90 days were still taking opioids five years later.¹⁴
7. Patients with mental health and substance abuse co-morbidities are more likely to receive COT than patients who lack these risk factors, a phenomenon referred to as *adverse selection*.¹⁵
8. Three large observational studies published in 2010 and 2011 found dose-related overdose risk in CNCP patients on COT.^{16,17,18}
9. COT at high doses is associated with increased risk of overdose death¹⁸, emergency room visits¹⁹ and fractures in the elderly²⁰.

There is no environmental impact associated with this Citizen’s Petition and we wish to be excluded under 21 CFR Sec. 25.24.

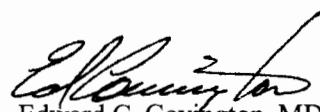
The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition (21 CFR Sec.10.30b).



Jane C. Ballantyne, MD, FRCA
UW Professor of Education and Research
Department of Anesthesiology and Pain Medicine
Seattle, Washington



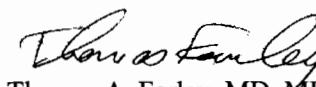
Russ Carlisle, MD
Medical Director, Emergency Department
Swedish Cherry Hill Medical Center
Seattle, Washington



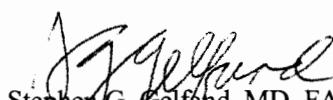
Edward C. Covington, MD
Director, Neurological Center for Pain
Cleveland Clinic
Cleveland, Ohio



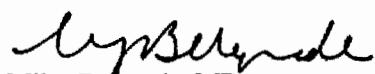
Richard A. Deyo, MD, MPH
Kaiser Permanente Professor of Evidence-Based
Family Medicine, Dept. of Family Medicine
Department of Medicine Director, OCTRI
Community and Practice Research Program
Oregon Health and Science University



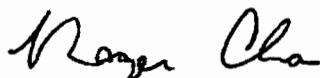
Thomas A. Farley, MD, MPH
Commissioner, Department of Health
City of New York



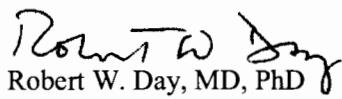
Stephen G. Gelfand, MD, FACP
Secretary, Physicians for Responsible Opioid
Prescribing
Myrtle Beach, South Carolina



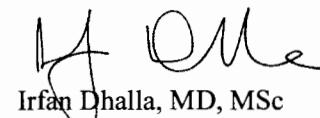
Miles Belgrade, MD
Medical Director, Fairview Pain Center
Adjunct Professor, Department of Neurology,
University of Minnesota Medical Center
Minneapolis, Minnesota



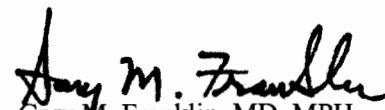
Roger Chou, MD, FACP
Associate Professor of Medicine
Dept. of Medicine and Dept. of Medical
Informatics and Clinical Epidemiology
Oregon Health & Science University



Robert W. Day, MD, PhD
President Emeritus
Fred Hutchinson Cancer Research Center
Seattle, Washington



Irfan Dhalla, MD, MSc
Assistant Professor, University of Toronto
Toronto, Ontario



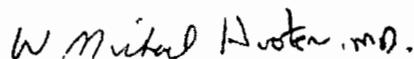
Gary M. Franklin, MD, MPH
Research Professor, University of Washington
Director, Occupational Epidemiology and Health
Outcomes Program
Seattle, Washington



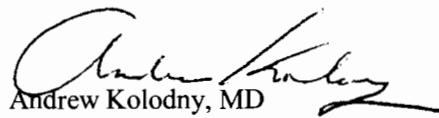
Stuart Gitlow, MD, MBA, MPH, FAPA
Acting President
American Society of Addiction Medicine
Chevy Chase, Maryland



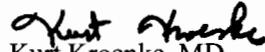
Roland W. Gray, MD, FASAM
Medical Director, Tennessee Medical Foundation
Physician's Health Program
Brentwood, Tennessee



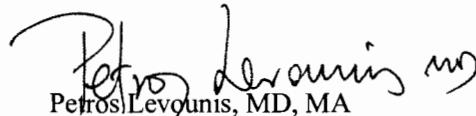
W. Michael Hooten, MD
Associate Professor of Anesthesiology
Mayo Clinic
Rochester, Minnesota



Andrew Kolodny, MD
President, Physicians for Responsible Opioid
Prescribing; Chair, Dept. of Psychiatry
Maimonides Medical Center
Brooklyn, New York



Kurt Kroenke, MD
Professor of Medicine, Indiana University Research
Scientist, VA HSR&D Center for Implementing
Evidence-Based Practice, Regenstrief Institute
Indianapolis, Indiana



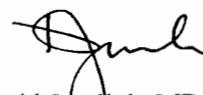
Petros Levounis, MD, MA
Director, The Addiction Institute of New York
Associate Chair for Clinical Services, Dept. of
Psychiatry, St. Luke's & Roosevelt Hospitals
New York, New York



Lewis Nelson, MD
Associate Professor, Dept. of Emergency Medicine
New York University School of Medicine
New York, New York



Erik Gunderson, MD, FASAM
Assistant Professor, Dept. of Psychiatry &
Neurobehavioral Sciences and Dept. of Medicine
Director, Clinical Pharmacological Research Unit
University of Virginia



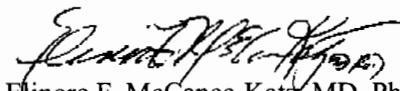
David Juurlink, MD, PhD
Head, Division of Clinical Pharmacology and
Toxicology, University of Toronto
Toronto, Ontario



Thomas R. Kosten, MD
Waggoner Chair and Professor of Psychiatry,
Neuroscience, Pharmacology
Baylor College of Medicine,
Michael E DeBakey VAMC
Houston, Texas



Eric B. Larson, MD, MPH
Vice President for Research, Group Health
Exec. Director, Group Health Research Institute
Seattle, Washington



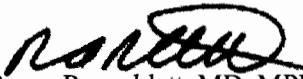
Elinore F. McCance-Katz, MD, PhD
Professor, Department of Psychiatry
University of California San Francisco
San Francisco, California



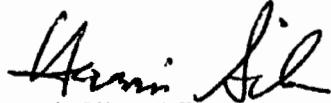
Rosemary Orr, MD
Professor of Anesthesiology, Seattle Children's
Hospital and University of Washington
Seattle, Washington



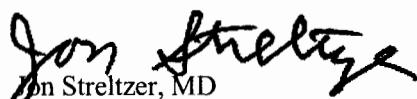
William Phillips, MD, MPH, FAAP
Theodore J. Phillips Endowed Professor in Family
Medicine, University of Washington
Seattle, Washington



Roger Rosenblatt, MD, MPH, MFR
Professor & Vice Chair, Dept. of Family Medicine
University of Washington School of Medicine
Seattle, Washington



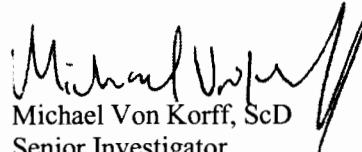
Harris Silver, MD
Policy Analyst, Senate Memorial 18 New Mexico
Drug Policy Task Force, Robert Wood Johnson
Foundation Center for Health Policy
University of New Mexico



Jon Strelitzer, MD
Program Director, Addiction Psychiatry
Professor of Psychiatry, University of Hawaii
Honolulu, Hawaii



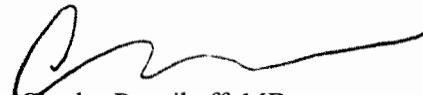
Barbara J. Turner MD, MSEd, MA, MACP
Professor of Medicine; Director, ReACH Center
Director, Health Outcomes Improvement
University of Texas Health Science Center
San Antonio, Texas



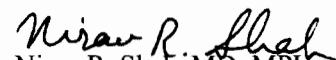
Michael Von Korff, ScD
Senior Investigator
Group Health Research Institute
Seattle, Washington



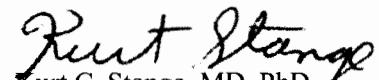
Art Van Zee, MD
Stone Mountain Health Services
St. Charles Clinic
Charles, Virginia



Charles Reznikoff, MD
Internal Medicine and Addiction Medicine,
Hennepin County Medical Center
Minneapolis, Minnesota



Nirav R. Shah, MD, MPH
Commissioner
New York State Department of Health
Albany, New York



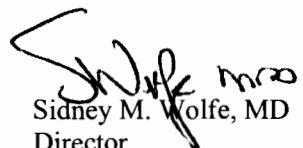
Kurt C. Stange, MD, PhD
Professor of Family Medicine & Community
Health, Epidemiology & Biostatistics, Oncology
and Sociology, Case Western Reserve University
Cleveland, Ohio



Mark Sullivan, MD, PhD
Professor, Dept. of Psychiatry and Behavioral
Sciences; Adjunct Professor Bioethics and
Humanities; Adjunct Professor, Anesthesiology
and Pain Medicine University of Washington
Seattle, Washington



Judith A. Turner, PhD
Professor, University of Washington, Dept. of
Psychiatry and Behavioral Sciences



Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group
Washington, DC

REFERENCES

1. Centers for Disease Control (CDC). Poison Issue Brief: Unintentional Drug Poisoning in the United States, 2007. Available online at <http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf>
2. Agency Medical Directors' Group. Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain. Washington State Agency Medical Directors' Group: 2010. Available online at <http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf>
3. Paone D, Dowell D, Heller D. Preventing misuse of prescription opioid drugs. City Health Information. 2011;30(4):23-30. Available online at <http://www.nyc.gov/html/doh/downloads/pdf/chi/chi30-4.pdf>
4. Hamburg MA. Innovation, regulation, and the FDA. N Engl J Med 2010;363:2228-2232.
5. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers—United States, 1999-2008. Morbidity and Mortality Weekly Report. 2011 Nov 1; 60:1-6.
6. U.S. General Accounting Office: Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem (GAO-04-110), Washington, DC, U.S. General Accounting Office, 2004
7. Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public health tragedy. Am J Public Health 2009;99:221-7.
8. Suffolk County Supreme Court Special Grand Jury. Grand Jury Report: CPL 190.85(1)(C): April 2012. Available online: <http://www.suffolkcountyny.gov/Portals/da/PDFs/webdoc/diversion%20and%20dissemination%20of%20controlled%20substances.pdf>
9. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C; American Pain Society – American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. J Pain 2009; 10:113-130.
10. Sullivan MD, Von Korff M, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. Pain. 2010 May;149(2):345-53.
11. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain. An epidemiological study. Pain 2006;125:172-9.
12. Boscarino JA, Rutstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system Addiction 2010; 105:1776-1782.
13. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30:185-194.
14. Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med. 2011;26(12):1450-1457.

15. Edlund MJ, Fan MY, DeVries A, Braden JB, Martin BC, Sullivan MD. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP Study. *Clin J Pain* 2010;26:1-8.
16. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of Internal Medicine* 2010;152:85-92.
17. Bohnert AS, Valenstein M, Bair MJ, et al. (2011). Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*, 305:1315-21.
18. Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med* 2011;171: 686-91.
19. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med* 2010;170:1425-32.
20. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med* 2010;25:310-5.